PCT/IB03/04873

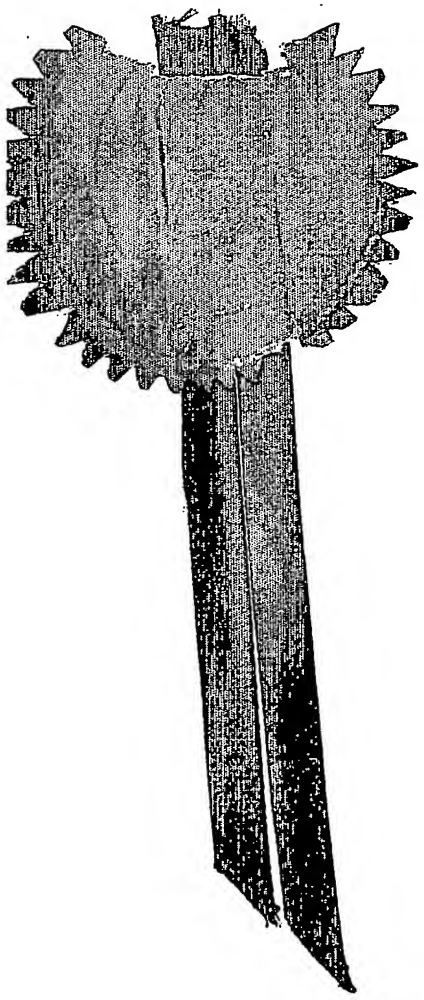
RU-298

सत्यमेव जयते

INTELLECTUAL PROPERTY INDIA

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY,
PATENT OFFICE, DELHI BRANCH,
W - 5, WEST PATEL NAGAR,
NEW DELHI - 110 008.

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application, Complete Specification*** *and* ***Drawing Sheets*** *filed in connection with Application for Patent No.**1095/Del/02** dated **31st October 2002.***



Witness my hand this 16th day of January 2004.

(S.K. PANGASA)
Assistant Controller of Patents & Designs

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

VCT/IB03/04873
RLL-298

सत्यमेव जयते

INTELLECTUAL PROPERTY INDIA

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY,
PATENT OFFICE, DELHI BRANCH,
W - 5, WEST PATEL NAGAR,
NEW DELHI - 110 008.

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application, Complete Specification*** *and* ***Drawing Sheets*** *filed in connection with Application for Patent No.**1095/Del/02** dated **31st October 2002.***

Witness my hand this 16th day of January 2004.

(S.K. PANGASA)
Assistant Controller of Patents & Designs

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

FORM 1

1008 DEL 02

31 OCT 2002

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 7, 54 and 135 and rule 33A)

1 We, **RANBAXY LABORATORIES LIMITED,** a Company incorporated under the Companies Act, 1956 of 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"PROCESS FOR THE PREPARATION OF NOVEL AMORPHOUS FORM OF LOSARATAN POTASSIUM"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. YATENDRA KUMAR

b. TARUN KANT SHARMA

c. PROSENJIT BOSE

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

DUPLICATE

4. That we are the assignee or legal representatives of the true and first inventors.

5. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18,
Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana).
INDIA.
Tel. No. (91-124) 6343126, 6342001 – 10
Fax No. (91-124) 6342027

6. Following declaration was given by the inventors in the convention country:

We, YATENDRA KUMAR, TARUN KANT SHARMA, PROSENJIT BOSE of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention in the convention country declare that the applicants herein, **Ranbaxy Laboratories Limited**, 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a. (YATENDRA KUMAR)

b. (TARUN KANT SHARMA)

c. (PROSENJIT BOSE)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Followings are the attachment with the application:

a. Complete Specification (3 copies)
b. Drawings (3 copies)
c. Statement and Undertaking on FORM – 3
d. Fee Rs.5,000/- (Rupees Five Thousand only..) in cheque bearing No. 685384-28-10-02 dated on **ANZ Grindlays Bank, New Delhi.**

We request that a patent may be granted to us for the said invention.

Dated this **28TH** day of **October, 2002.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary

FORM 2

The Patents Act, 1970

(39 of 1970)

COMPLETE SPECIFICATION

(See Section 10)

PROCESS FOR THE PREPARATION OF NOVEL AMORPHOUS FORM OF LOSARTAN POTASSIUM

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention relates to a process for the preparation of novel amorphous form of losartan potassium .

Losartan potassium is chemically, 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imida. zole-5-methanol and has structural Formula I, as shown in the accompanied drawings. It is disclosed in US patent No. 5,138,069 assigned to Du Pont. Losartan potassium is a substituted imidazoles useful as angiotensin II blockers. It is known for treating hypertension and congestive heart failure.

The difference in the activity of different polymorphic forms of a given drug has drawn the attention of many workers in recent years. This has especially become very interesting after observing that many antibiotics, antibacterials, tranquilizers etc. exhibit polymorphism and some of the polymorphic forms of a given drug exhibit superior bioavailabiltiy and consequently show much higher activity compared to the polymorphs. The term polymorphism includes different physical forms, crystal forms, crystalline / liquid crystalline / non-crystalline (amorphous) forms.

It has also been disclosed that the amorphous forms in the number of drugs exhibit different dissolution characteristics and in some cases different bioavailability patterns compared to the crystalline form [Konne T. Chem Pharm Bull 38, 2003 (1990)]. For some therapeutic indications one bioavailability pattern may be favoured over another. Cefuroxime axetil is the classical example of amorphous form exhibiting higher bioavailibility than the crystalline form. Host of patents have been granted on a number of drugs exhibiting polymorphism.

US Patent No. 5,608,075 discloses novel crystalline forms of losartan potassium and reports two novel polymorphic forms, differing from one another in respect of their physical properties, stability, spectral data. They are designated Form I and Form II. However, there is no teaching of the amorphous form of losartan potassium in the known prior art.

We reasoned that the amorphous form of losartan potassium would have an even better intrinsic dissolution and therefore, set out to prepare in this invention, hitherto unknown, solid amorphous form of losartan potassium.

The present invention relates to a new losartan potassium, the amorphous form and a process for the preparation thereof. The present process uses conditions which are convenient to perform on a commercial scale, operationally safe and provide the product in pure form . The process provides obvious benefits with respect to safety, health and environmental consideration.

Accordingly, the present invention provides an amorphous form of losaratan potassium and a process for preparation thereof. The process comprises dissolving losartan potassium in a suitable solvent(s), water or mixtures thereof and recovering amorphous form by a conventional technique. Such conventional techniques include, but are not limited to distillation, distillation under vacuum, evaporation spray drying, freeze drying etc.

In a preferred embodiment of the invention losartan potassium is recovered from solution in an amorphous form using a spray drying technique. The mini-spray dryer (Model : Buchi type) which is used, operates on the principle of nozzle spraying in a parallel flow i.e. spray product and drying gas flow in the same direction. The drying gas carbon air or inert gas car be air or inert gases such as nitrogen, argon and carbon dioxide. Nitrogen is preferred in this case.

The term "suitable solvent" means lower alkanols, ketones, chlorinated solvents or mixtures thereof. Lower alkanols include those primary, secondary and tertiary alcohols having one to six carbon atoms preferably selected from primary, secondary and tertiary alcohols having one to four carbon atoms such as methanol, ethanol, n-propyl alcohol, isopropyl alcohol, isobutanol, n-butanol, t-butanol or mixtures thereof.

In a more preferred embodiment methanol is used.

The process of the said invention also includes various solvates of losartan potassium and its conversion to amorphous losartan potassium

Figure 1 is an infrared spectrum showing peaks characteristic of amorphous losartan potassium.

Figure 2 is an X- ray powder diffraction (XRD) pattern of amorphous losartan potassium.

Figure 3 is an infrared spectrum showing peaks characteristic of crystalline form I and form II of losartan potassium from 1150 cm^{-1} to 600 cm^{-1} obtained per U.S. patent No. 5,608,075: (A) Form I and (B) Form II .

Figure 4 is an infrared spectrum showing peaks characteristic of crystalline form I and form II of losartan potassium from 1800 cm^{-1} to 1150 cm^{-1} obtained per U.S. patent No. 5,608,075: (A) Form I and (B) Form II .

Figure 5 is an XRD pattern characteristic of crystalline form I and form II of losartan potassium obtained per U.S. patent No. 5,608,075 : (A) Form I and (B) Form II .

Figure 2 shows no peak which are characteristic of crystalline losartan potassium form I and form II (Figure 5 and 6 of the accompanied drawings) showing the form to be an amorphous one.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

EXAMPLE

A suspension was made from crystalline losartan potassium (10 g) in methanol (300 ml) at ambient temperature. The resulting solution was slowly heated to 45-47°C for 30 minutes to get a clear solution which was subjected to spray drying on 190 Mini Spray Dryer (Buchi make) at a temperature of 67-68°C using nitrogen gas. The losartan potassium in an amorphous form was collected. It was further dried at 45-50°C for 8 hours under vacuum to yield was found to be amorphous.

X- ray powder diffraction (XRD) pattern (Figure 2) does not exhibit any peak and shows a plain halo thus demonstrating the amorphous nature of the product. Infrared spectrum in KBr (Figure 1) is different than one obtained for crystalline form of losartan potassium.

WE CLAIM:

1. A process for the preparation of losartan potassium in amorphous form which comprises dissolving crystalline losartan potassium in suitable solvent(s), water or mixtures thereof and recovering losartan potassium in the amorphous form from the solution thereof.

2. The process of claim 1 wherein suitable solvent(s) is selected from lower alkanols, , ketones, chlorinated solvents or mixtures thereof.

3. The process of claim 2 wherein lower alkanols includes primary, secondary and tertiary alcohols having from one to six carbon atoms.

4. The process of claim 2 wherein lower alkanols includes primary, secondary and tertiary alcohols having from one to four carbon atoms.

5. The process of claim 4 wherein lower alkanols is selected from methanol, ethanol, n-propyl alcohol, iso propyl alcohol, isobutanol, n-butanol, t-butanol or mixtures thereof.

6. The process of claim 5 wherein the solvent is methanol.

7. The process of claim 1 wherein the solvent is removed by a conventional technique.

8. The process of claim 7 wherein the conventional technique includes distillation, distillation under vacuum, evaporation, spray drying or freeze drying.

9. The process of claim 8 wherein losartan potassium in an amorphous form is recovered by spray drying.

10. The process of claim 9 wherein the spray drying is effected in the presence of nitrogen gas.

11. The process of claim 1 wherein the product obtained is further dried.

12. A process for the preparation of losartan potassium in amorphous form of structural formula I shown in the accompanied drawings substantially described herein and exemplified by the example

Dated this 30TH day of **October, 2002.**

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

Ranbaxy Laboratories Limited

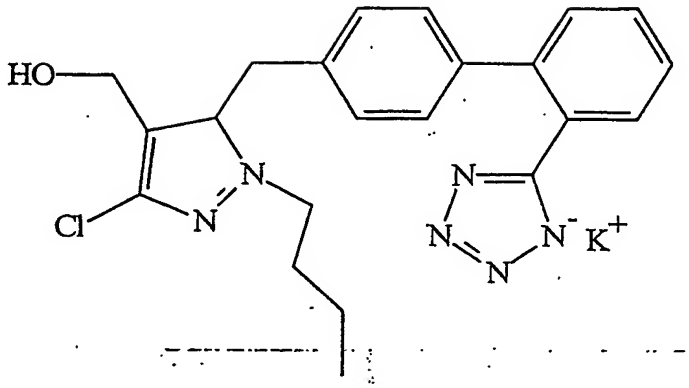
Application No.

No. of sheets = 06

Sheet 01 of 06

1095 DEL 02

31 OCT 2002



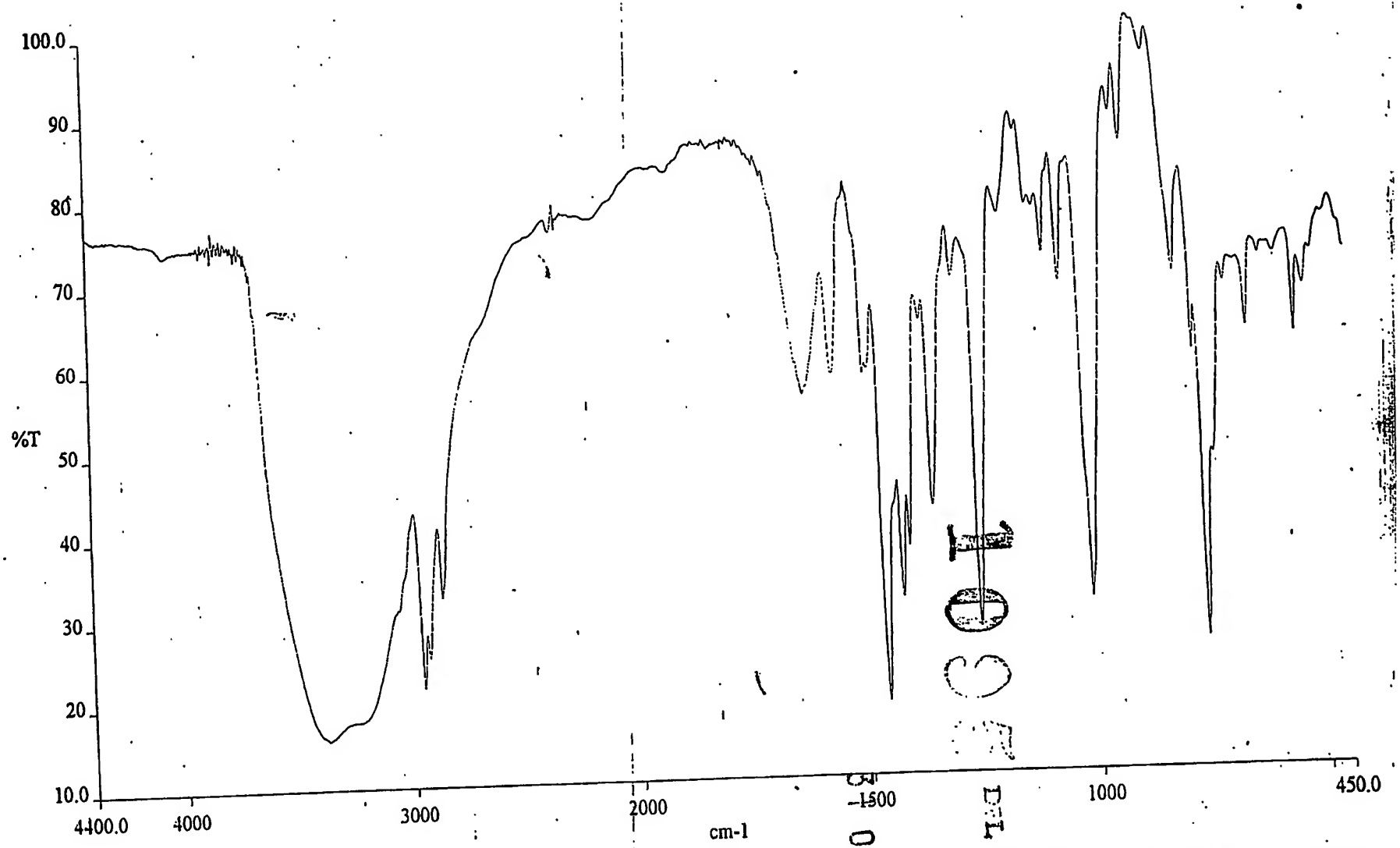
FORMULA 1

DUPLICATE

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

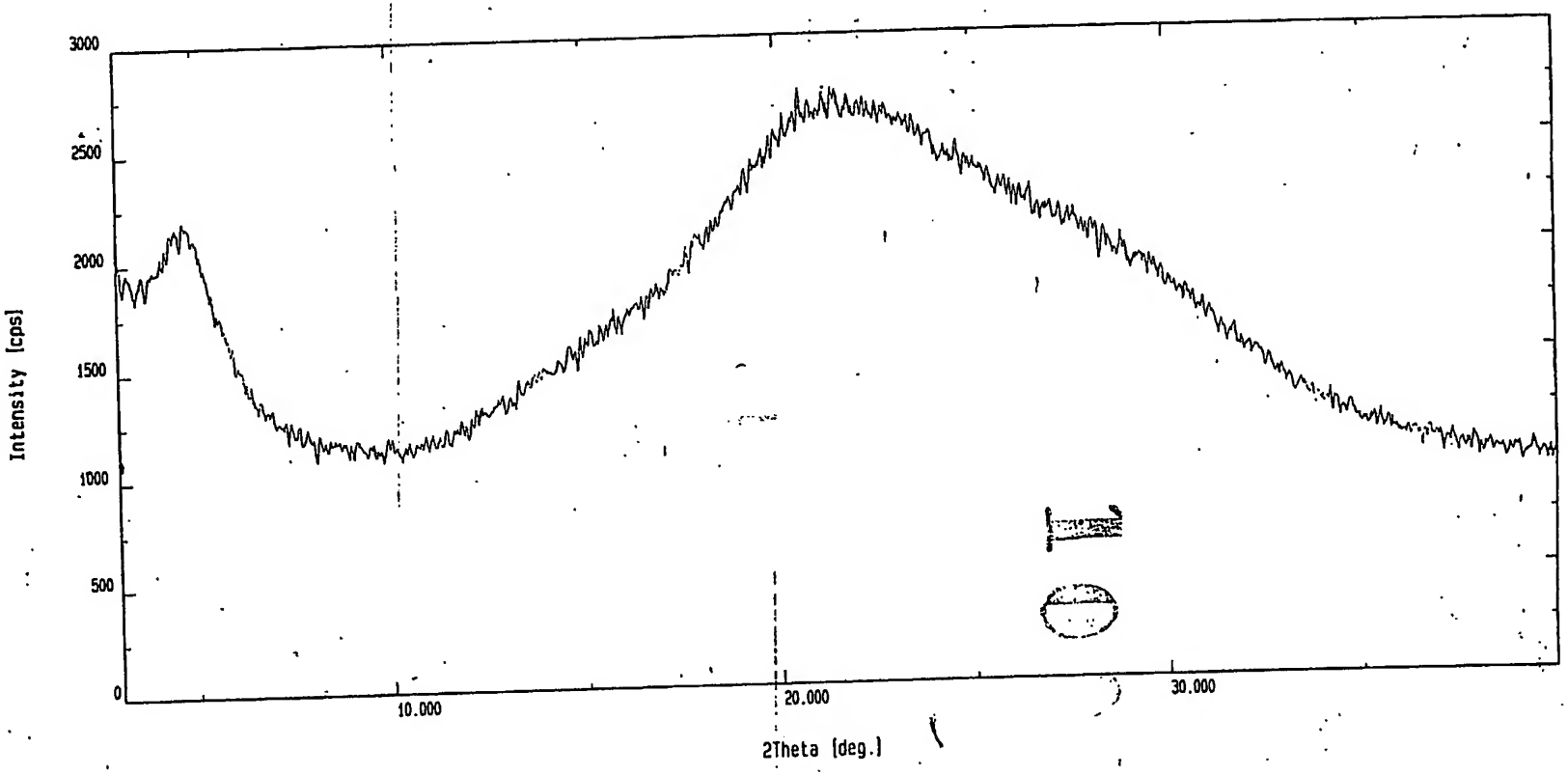
FIGURE 1



For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

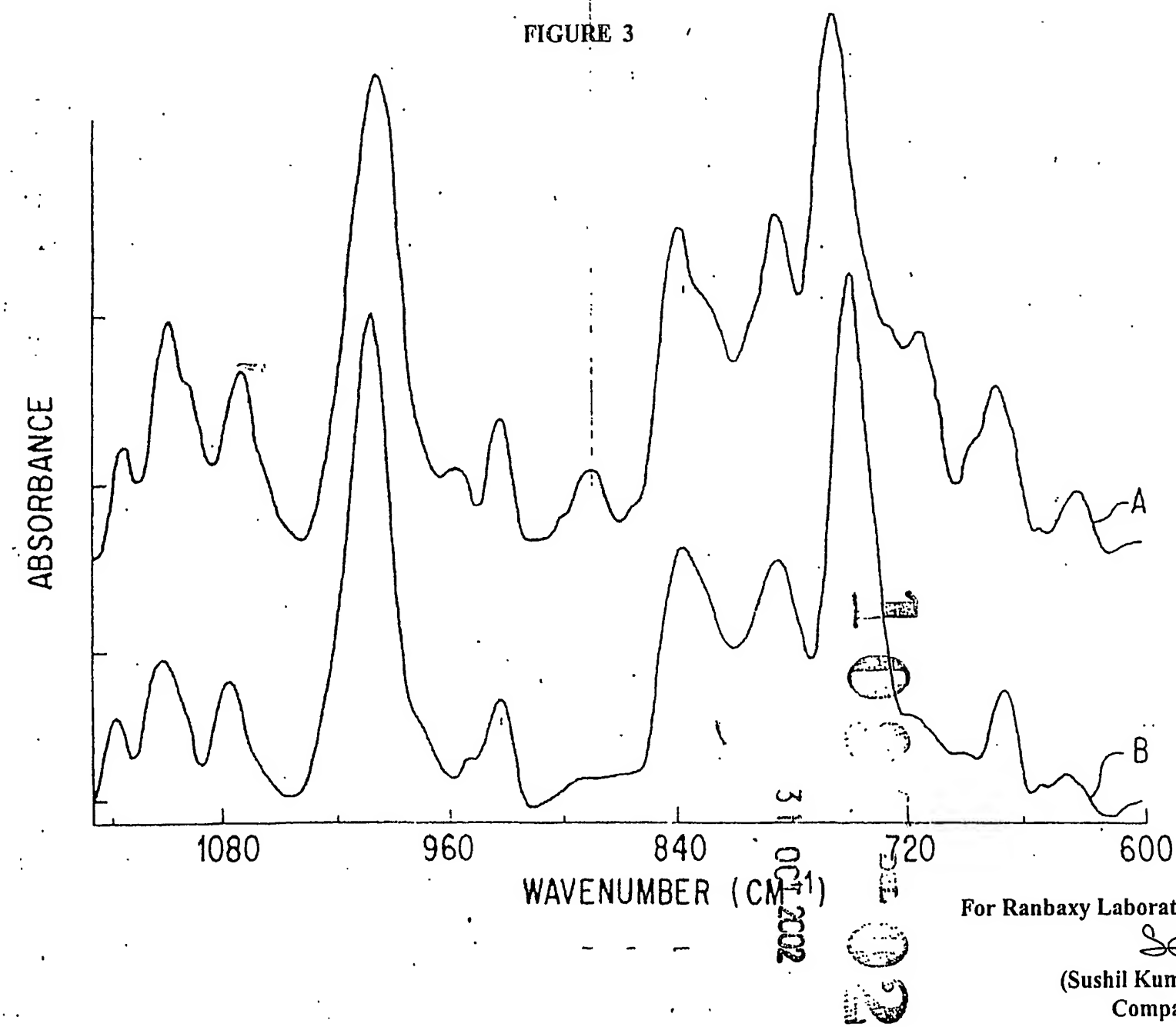
DUPLICATE FIGURE 2



For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

FIGURE 3

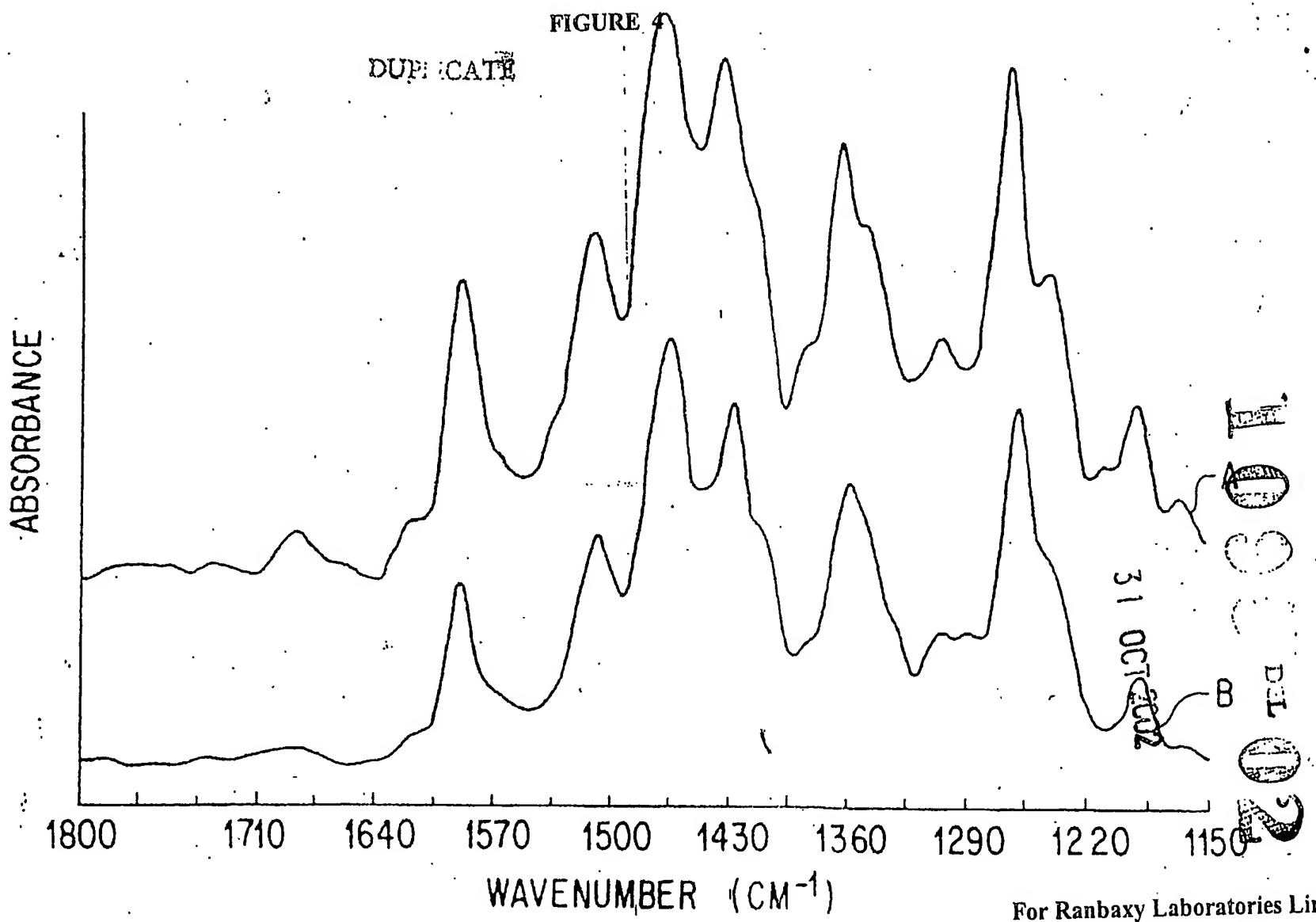


For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

FIGURE 4

DUPLICATE



For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

FIGURE 5

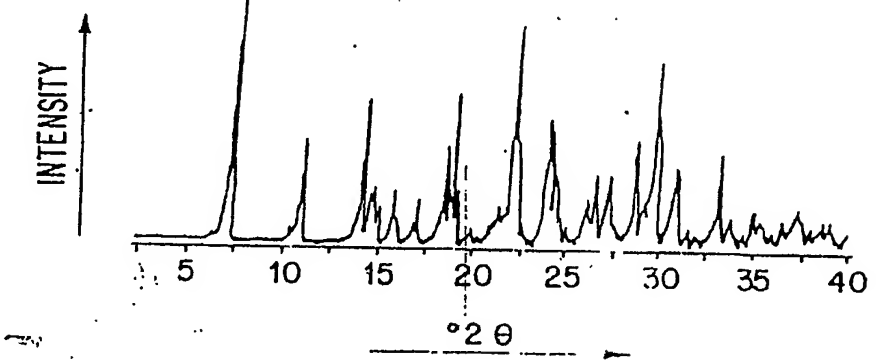


FIG. 5A

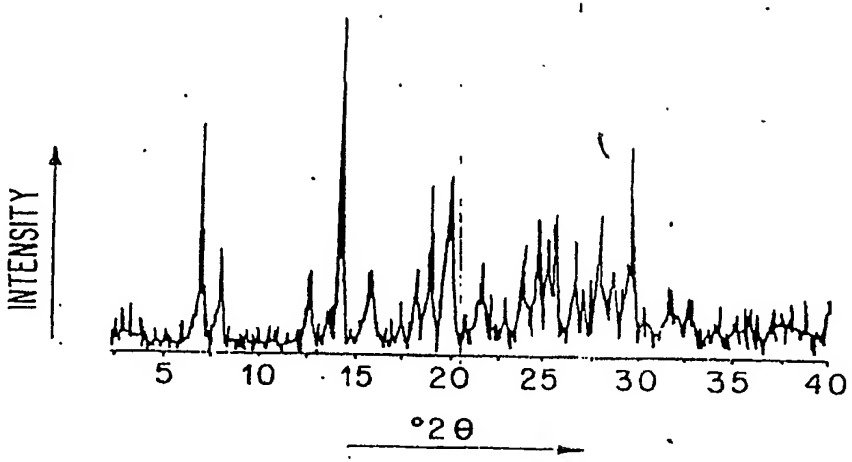


FIG. 5B

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary